Challenges in Pathologic Staging of Renal Cell Carcinoma: A Study of Interobserver Variability Among Urologic Pathologists

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Challenges in Pathologic Staging of Renal Cell Carcinoma

A Study of Interobserver Variability Among Urologic Pathologists

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Abstract: Staging criteria for renal cell carcinoma differ from many other cancers, in that renal tumors are often spherical with subtle, finger-like extensions into veins, renal sinus, or perinephric tissue. We sought to study interobserver agreement in pathologic stage categories for challenging cases. An online survey was circulated to urologic pathologists interested in kidney tumors, yielding 89% response (31/35). Most questions included 1 to 4 images, focusing on: vascular and renal sinus invasion (n = 24), perinephric invasion (n = 9), and gross pathology/specimen handling (n = 17). Responses were collapsed for analysis into positive and negative/equivocal for upstaging. Consensus was regarded as an agreement of 67% (2/3) of participants, which was reached in 20/33 (61%) evaluable scenarios regarding renal sinus, perinephric, or vein invasion, of which 13/33 (39%) had $\geq$80% consensus. Lack of agreement was especially encountered regarding small tumor protrusions into a possible vascular lumen, close to the tumor leading edge. For gross photographs, most were interpreted as suspicious but requiring histologic confirmation. Most participants (61%) rarely used special stains to evaluate vascular invasion, usually endothelial markers (81%). Most agreed that a spherical mass bulging well beyond the kidney parenchyma into the renal sinus (71%) or perinephric fat (90%) did not necessarily indicate invasion. Interobserver agreement in pathologic staging of renal cancer is relatively good among urologic pathologists interested in kidney tumors, even when selecting cases that test the earliest and borderline thresholds for extrarenal extension. Disagreements remain, however, particularly for tumors with small, finger-like protrusions, closely juxtaposed to the main mass.

Key Words: renal cell carcinoma, pathologic staging, vein invasion, renal sinus invasion, perinephric invasion

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Staging of renal cell carcinoma differs somewhat from the prototypical cancer, in that expanding tumors do not necessarily elicit desmoplastic or destructive infiltrative response. Rather, renal cell carcinoma tumors are largely rounded or spherical, with stage categories defined based on extension into the renal sinus, perinephric fat, and renal veins.[1,2] Specific findings indicating higher pathologic pT stage are potentially more subtle than those of tumors in other organs. Nonetheless, pathologic staging may have substantial importance for determining clinical follow-up schedules, patient counseling, and enrollment in clinical trials for patients harboring higher-risk renal cancers. In this study, we sought to assess the extent of interobserver variability in assigning pathologic stage variables in renal cell carcinoma, with emphasis on testing the earliest and borderline thresholds for higher stage categories.

METHODS

After approval of the study by the institutional review board of the Henry Ford Health System, an online survey was designed by 4 of the authors (S.R.W., P.R., M.B.A., and K.T.) to query pathologic stage scenarios in renal cancer, using the SurveyMonkey platform (SurveyMonkey.com, Palo Alto, CA) in an institutional HIPAA-secure account. Thirty-five pathologists were invited to participate, based on a perceived and demonstrated interest in tumors of the kidney, with attempt to capture a broad geographic distribution and including both senior and more recently trained specialist urologic pathologists. Complete responses were received from 31/35 invited (89%). Of the remaining 4, 1 responded but declined to participate, 1 did not complete the entire survey, and 2 did not respond, all of which are excluded from the following data. All participants agreed to coauthor the resulting manuscript.

Most questions included 1 to 4 images, focusing on: vascular and renal sinus invasion (n = 24), perinephric invasion (n = 9), and gross pathology/specimen handling (n = 17). For the purposes of analysis, the 33 questions corresponding to renal sinus and perinephric invasion could be studied for consensus interpretation, which was defined as 2/3 (67%) agreement in favor of or against higher stage. Cases were also assessed for a strong consensus, if $\geq 80\%$ agreement in favor of or against a higher stage category. Interpretations were collapsed into positive for the higher stage category and negative or equivocal, since there was often varied interpretation of renal sinus or renal vein invasion, or both, yet all resulting in the same pT3a stage category. Equivocal responses (suspicious but not definitive for higher stage), were included in the negative category, considering the American Joint Commission on Cancer (AJCC) recommendations that equivocal cases default to the lower of the 2 considerations.[3] Questions focusing on gross pathology were largely not amenable to assigning consensus diagnoses, as most responses indicated that the findings were suspicious for invasion, but that histologic confirmation was required. Therefore, these and other general questions were not counted in the denominator for consensus. On the basis of knowledge that tumor histologic subtypes have different growth patterns, including variable extension beyond the tumor pseudocapsule (more common in papillary renal cell carcinoma)[4] and that some benign neoplasms may have intravascular growth,[5–7] a set of questions also queried whether the participants believe that staging parameters may have different relevance based on tumor subtype.

RESULTS

Brief summaries of the focus and responses of each question are included in Supplemental File 1 (Supplemental Digital Content 1, http://links.lww.com/PAS/A634). Participants represented the United States (n = 21), Canada (n = 2), Australia, Czech Republic, Italy, Japan, New Zealand, Switzerland, Spain, and United Kingdom (1 each). Consensus of 67% (2/3) was reached in 20/33 (61%) evaluable scenarios regarding renal sinus, perinephric, or vein invasion, of which 13/33 (39%) had $>80\%$ consensus. Challenging cases for potential early vein branch invasion are shown in Figure 1. In the context of a tumor outpouching or finger-like protrusion possibly corresponding to a vein, interpretation as pT3a increased when the possible venous structure demonstrated a more robust lumen and when it was juxtaposed to renal sinus fat (Fig. 2) or within renal sinus (Fig. 3). Scenarios demonstrating direct soft tissue extension into the renal sinus (questions 20 to 25 in Supplemental File 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A634, Figs. 4A, B) all reached consensus for renal sinus invasion.

When queried as to the presence of a fibromuscular rim associated with potential intravascular tumor (Fig. 4C), responses approached but did not reach consensus as to whether this type of smooth muscle argues against vascular invasion (35%) or does not affect the interpretation (65%), that is, tumor can bring vein wall with it and still represent vein invasion. Additional comments by participants indicated that this would depend on the context and size of the structure in question. When asked if a layer of such tissue contains compressed normal structures, such as glomeruli or nonneoplastic tubules, there was 97% agreement that this argued against invasion.

One example of papillary renal cell carcinoma with a few tubules extending into loose tissue at the perinephric interface in the setting of possible previous biopsy artifact was interpreted as not definitive for invasion (68%); however, for the same case, responses shifted to consensus agreement (74%) regarding pT3a stage, assuming there had not been a prior biopsy. Regarding specific criteria for interpreting histologic features as biopsy site artifact, only 48% reported having specific criteria in this setting. Free text responses included presence of hemosiderin or hemorrhage (n = 9), confirmed history of biopsy (n = 7), and linear distribution of the tumor (n = 5). A minority of participating responders indicated that they interpret fat invasion differently for papillary renal cell carcinoma (19%) compared with clear cell renal cell carcinoma, and 42% reported that they believe that staging parameters are

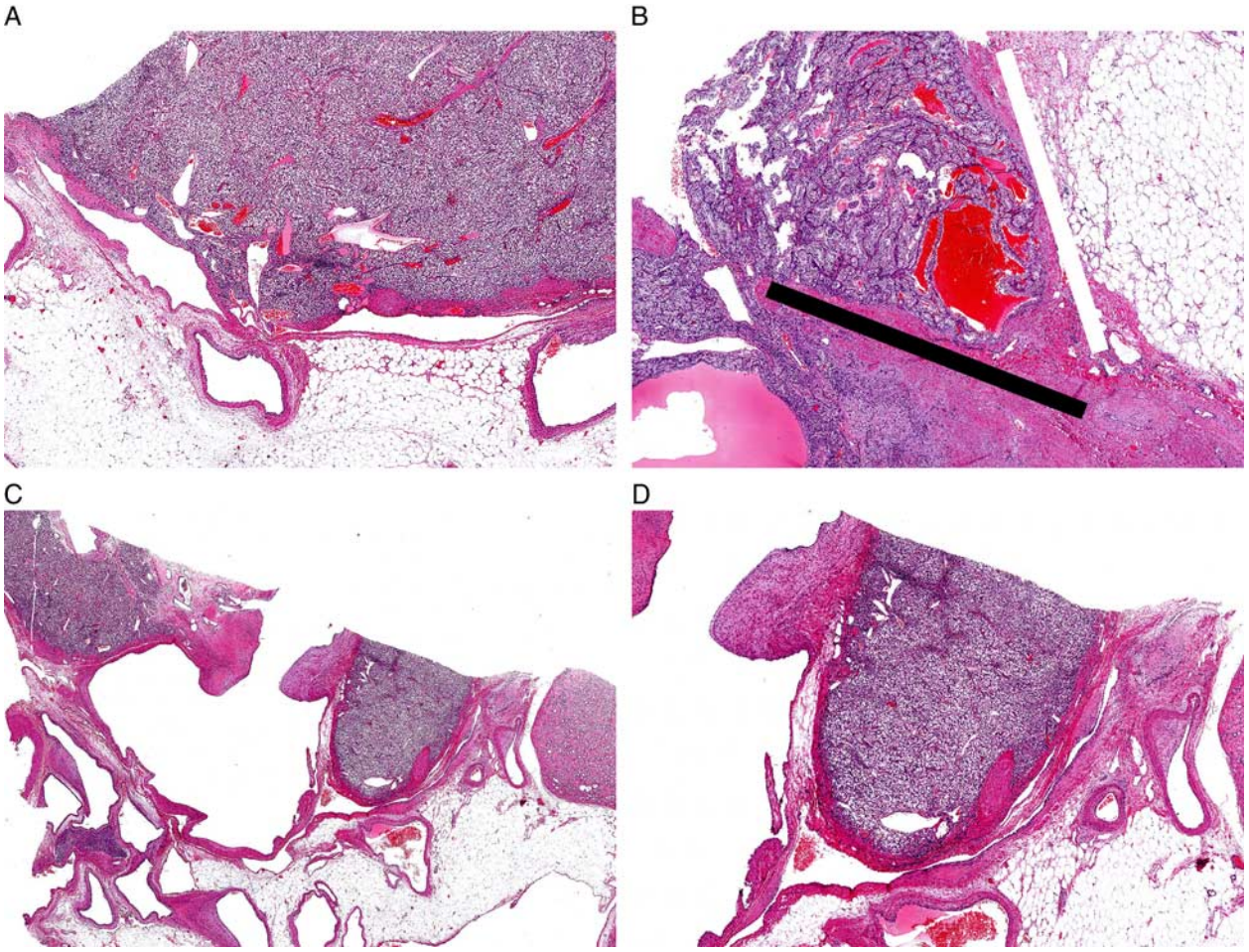

FIGURE 1. Challenging cases for potential early vein branch or renal sinus invasion: A, A selected image from question 3 demonstrates a clear cell renal cell carcinoma tumor that abuts and indents a large vein at the hilum. This example had no consensus for pT3a (52% yes, 48% no/equivocal). B, A selected image from question 5 demonstrates a clear cell renal cell carcinoma tumor that extends beyond 1 fibromuscular plane (black line) but is separated from the hilar fat by a second fibromuscular plane (white line). This example had no consensus for pT3a (42% yes, 58% no/equivocal). C and D, Two images from question 4 demonstrate a clear cell renal cell carcinoma tumor with tumor nodules that extend into hilar vascular tissue with rounded to elongated finger-like extension. This example had no definite consensus for pT3a (61% yes, 39% no/equivocal).

less relevant to chromophobe renal cell carcinoma. However, only 3% indicated using different thresholds for invasion chromophobe renal cell carcinoma (Fig. 4D).

For gross pathology images, the most common response was that the findings were suspicious for upstaging (48% to 68%) but that histologic confirmation is required (Fig. 5A). Therefore, these were excluded from considering a consensus diagnosis, as the ambiguous category was the most common response. When prompted that gross findings are convincing for vein invasion, 58% of participants were willing to interpret the tumor as pT3a, even if the histologic sections did not clearly demonstrate a vascular lumen, whereas 26% were not, and 16% gave and "other" response listing additional strategies, including submitting additional sections, preparing additional section levels, or using additional stains to confirm the vascular lumen.

Regarding interpretation of the vein margin, consensus (68%) was that histologic confirmation of tumor adherent to the margin is required for diagnosis of a positive vein margin. When asked if intravascular tumor extends beyond the vein margin, 3% interpreted this as always a positive margin, 6% considered it to depend on gross evaluation of attachment, and 90% required microscopic confirmation of attachment to the vein wall. When shown a round tumor bulging into the renal sinus (Fig. 5B) or perinephric fat (Fig. 5C), there was a consensus that this did not necessarily indicate invasion (71% and 90%, respectively, for renal sinus and perinephric tissue). Microscopically, a relatively large rounded nodule appearing possibly separate from the tumor did not reach consensus for perinephric invasion (Fig. 5D). Regarding a renal tumor composed of a large unilocular cyst with a single nodule of solid tumor in 1 wall of the cyst, 71%

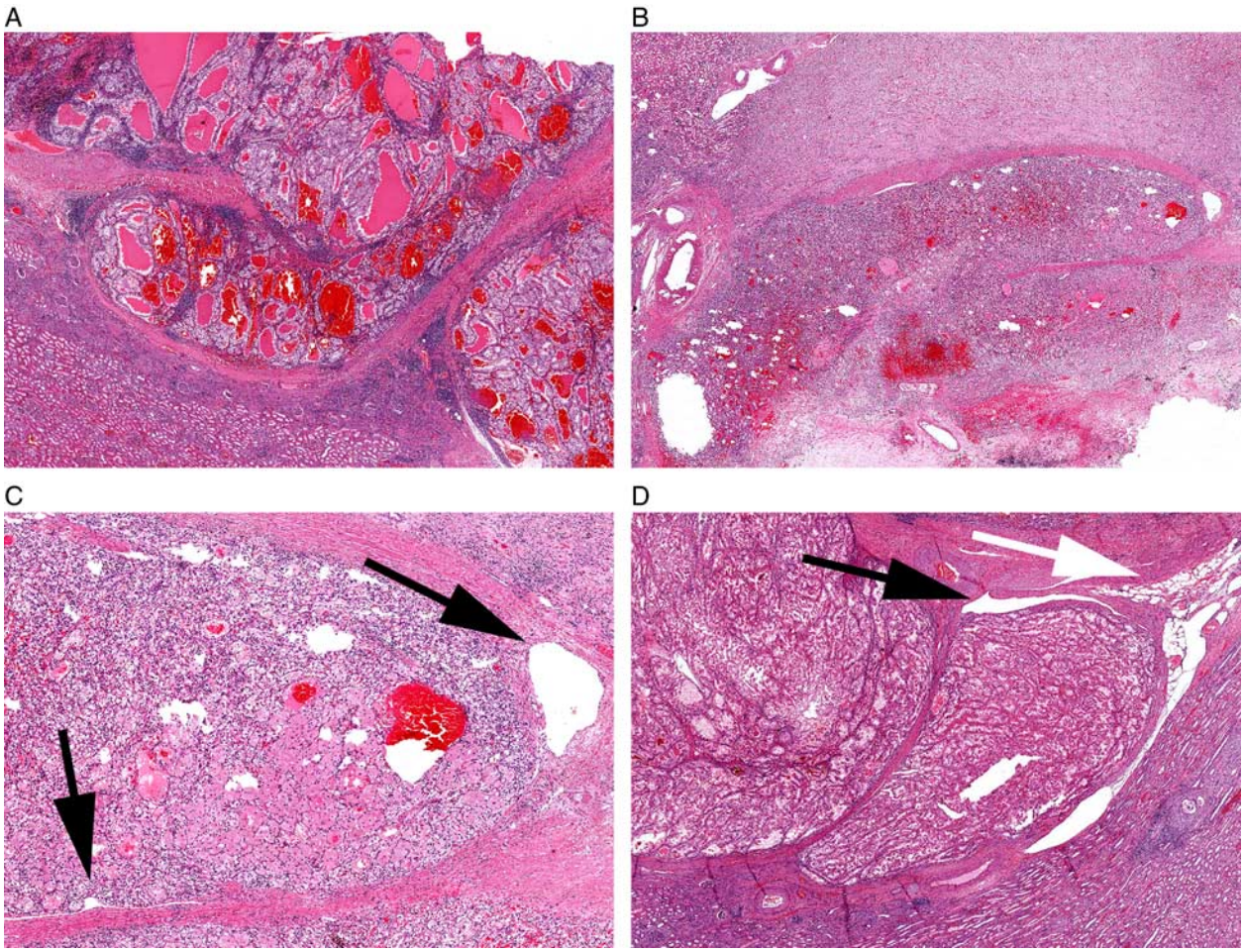

FIGURE 2. Challenging cases for potential intrarenal early vein branch invasion: A, A selected image from question 7 demonstrates a clear cell renal cell carcinoma tumor with a finger-like extension that herniates beyond the fibromuscular pseudocapsule of the tumor. This example had consensus against pT3a (6% yes, 94% no/equivocal). B and C, Selected images from question 10 demonstrate another finger-like extension away from the mass, but still within the kidney. In contrast to question 7, there is a focal possible vascular lumen (C, arrows). This example had consensus against pT3a, but with a higher fraction of participants interpreting as vein invasion (29% yes, 71% no/equivocal). D, A selected image from question 12 demonstrates a clear cell renal cell carcinoma tumor with a finger-like extension. This example includes a possible vein lumen (black arrow) and focal renal sinus fat (white arrow). Interpretation shifted in favor of pT3a for this case but did not reach consensus (58% yes, 42% no/equivocal).

would base the tumor size on the combined size of the cyst and the tumor, only if the cyst has a lining similar to the neoplastic cells in the solid component. The minority would use the larger size (cyst+mass) regardless of the appearance of the cyst lining (16%) or the smaller size, regardless of the cyst lining (3%). The remaining 10% gave a write-in response that they would note both sizes in a comment, of which two would use the larger size and one did not specify.

Most participants only rarely used special stains for diagnosis of vascular invasion (61%), which were reported to most commonly be endothelial immunohistochemical markers (81%), followed by muscle markers (35%), elastic stain (27%), or trichrome stain (15%). Regarding the phenomenon of retrograde venous invasion,[8] 48% reported being comfortable with recognizing this finding, and 26% document its presence in their reports, whereas 48% classify it as pT3a, but do not specifically document it. The remaining found it difficult to assess it in practice (16%) or reported being not familiar with it (6%). Of note, as multiple responses were allowed for this question, the percentages do not sum to 100%.

The most recent, 8th edition of the AJCC staging system has removed the previous requirements that renal vein branch invasion be identified grossly and that the vein must contain muscle to be considered as such.[2] Most participants reported that they had previously classified cases without strictly using these criteria. For example, when invasion was either not recognized grossly, or the muscle was inconspicuous, the case was still staged pT3a (84%). Conversely, 16% reported that this would introduce a change in their practice, because they had refrained from interpreting these as pT3a previously.

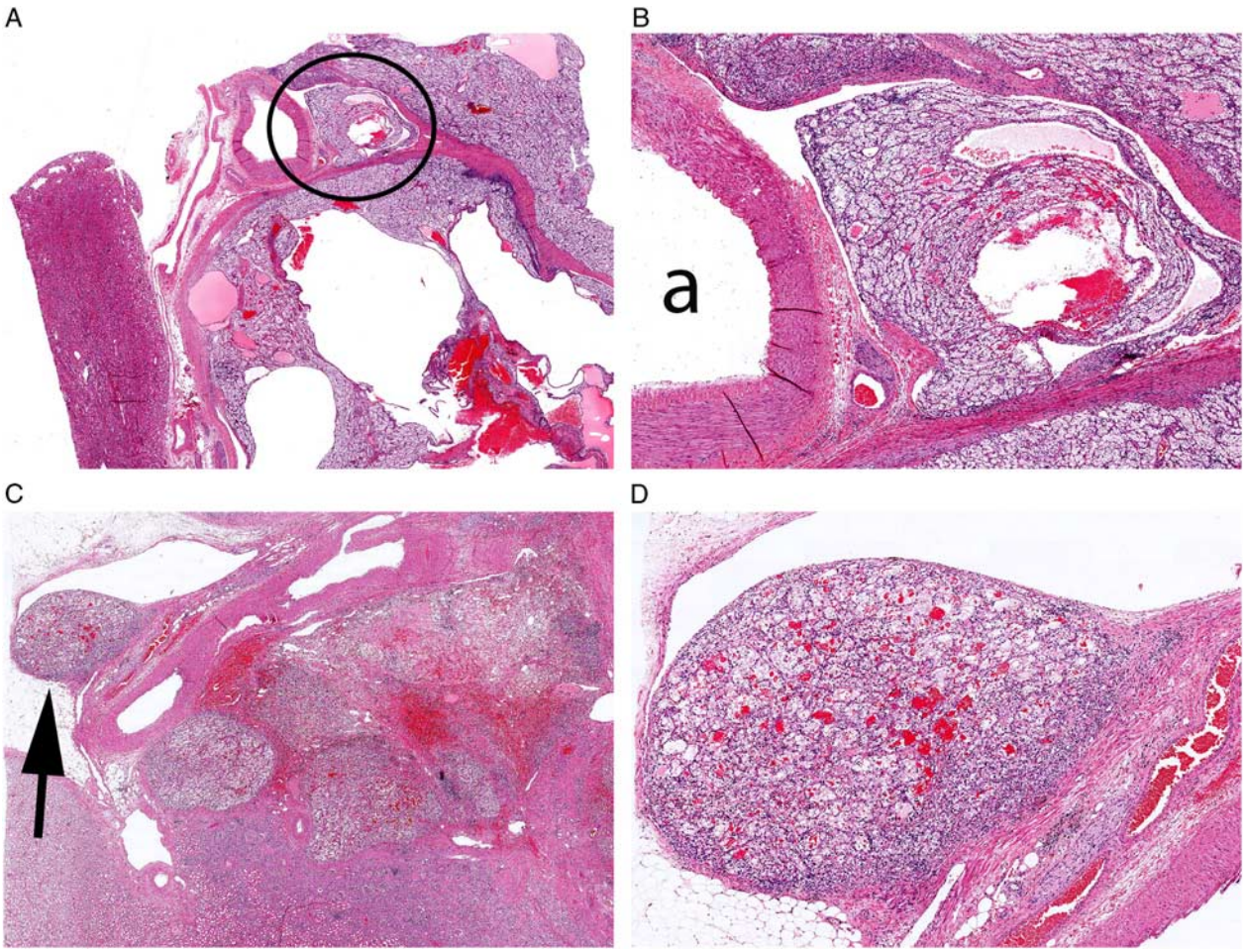

FIGURE 3. Cases with high agreement for pT3a. A and B, Selected images from question 16 demonstrate a clear cell renal cell carcinoma tumor with a polypoid nodule loosely connected within a vascular space (A, circled). Higher magnification reveals the paired artery (a) and tumor nodule within accompanying vein. This example reached consensus in favor of pT3a (84% yes, 16% no/equivocal). C and D, Selected images from question 11 demonstrate a clear cell renal cell carcinoma tumor with a polypoid nodule protruding into a renal sinus vein (A, arrow and B). This example reached consensus in favor of pT3a (94% yes, 6% no/equivocal).

When comparing pathologists in the United States to those of other countries, there were 9 questions for which the overall response for or against increased stage was markedly different between groups (shown in Supplemental File 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A634). However, a specific theme could not be discerned regarding the nature of these cases. In 6, the non-US pathologists were more strongly in favor of a higher stage, whereas in 1, the US pathologists were more strongly in favor of higher stage. In another, the US pathologists were more uniformly against higher stage (90%), whereas the non-US group was more equivocal (40%/60%). For the question regarding the new AJCC criteria for vein involvement, the US pathologists predominantly indicated that they were already using the updated criteria (95%) more than the non-US pathologists (60%).

DISCUSSION

The criteria for staging and invasion (vascular, perinephric fat, renal sinus) of kidney tumors have been previously addressed by the urologic pathology community at the 2012 International Society of Urological Pathology Consensus (ISUP) Consensus Conference and specific recommendations were issued regarding handling and staging of renal cell carcinoma.[1] Therefore, this survey represents the first major attempt to evaluate the application of specific staging criteria in nonstraightforward scenarios, or scenarios which have not been previously covered by specific guidelines, in a geographically diverse population of urologic pathologists.

Renal cell carcinomas represent a group of tumors that often manifest invasion with rounded tumor outpouchings and extension into vascular structures, carrying an intact endothelial cell layer.[9] Therefore, the criteria for

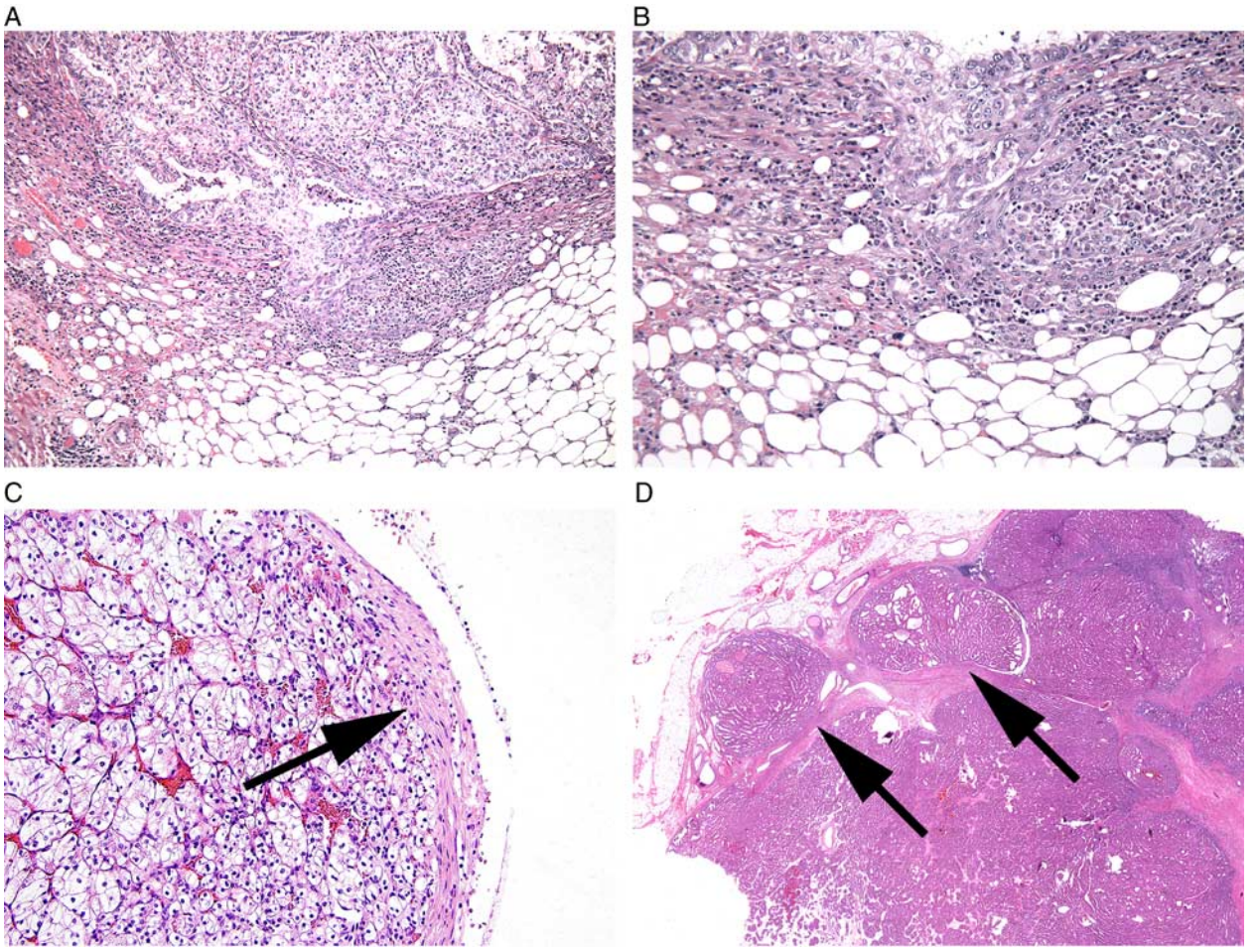

FIGURE 4. Scenarios for direct renal sinus invasion and other situations: A and B, The 2 images provided to participants from question 22 show tumor cells from a clear cell renal cell carcinoma extending into renal sinus fat. This example reached consensus for pT3a (97% yes, 3% no/equivocal). C, A representative image from question 26 shows a possible intravascular tumor with a layer of smooth muscle tissue at the edge (arrow). This question approached but did not reach consensus as to whether this type of smooth muscle argues against vascular invasion (35%) or does not affect the interpretation (tumor can bring vein wall with it and still represent vein invasion, 65%). D, This selected image from question 28 shows eosinophilic chromophobe renal cell carcinoma with multinodular growth bulging into perinephric fat (arrows). This question did not reach consensus for pT3a (61% yes, 39% no/equivocal).

assessing invasion are potentially different from the prototypical cancer (crab-like), with infiltrative growth and desmoplastic reaction. In this study we aimed to evaluate whether urologic pathologists use similar thresholds for invasion, especially in cases that test the earliest or borderline thresholds for increasing the pathologic stage categories.

We found that overall agreement for or against pT3a is relatively good among the urologic pathologists interested in kidney cancer, with a substantial number of cases (20/33 specific evaluable scenarios) reaching two thirds consensus (67%). Of these, 13 had a strong consensus of >80% (Table 1). Still some scenarios exist that did not reach complete agreement in our cohort, especially when the tumor extension into a putative vein branch remains within the kidney parenchyma, and when there is unclear evidence of the vein lumen (Figs. 1, 2). When tumor is in direct contact with the renal sinus fat, agreement was good (Fig. 4).

This study provides some potential guidance (based on subspecialty opinion) for a few areas of uncertainty that, to our knowledge, have not been specifically addressed in the previous staging recommendations. Consensus was approached but not reached as to whether a smooth muscle layer at the edge of the intravascular tumor is compatible with venous invasion (65%). That is, can a tumor bring part of the smooth muscle of the vein wall with it, yet still be invasive? Despite not reaching a consensus, resolving this in practice may be facilitated by other strategies, such as critically reassessing the gross appearance or evaluating additional section levels or special stains. These may increase pathologists' confidence (or lack thereof) that such

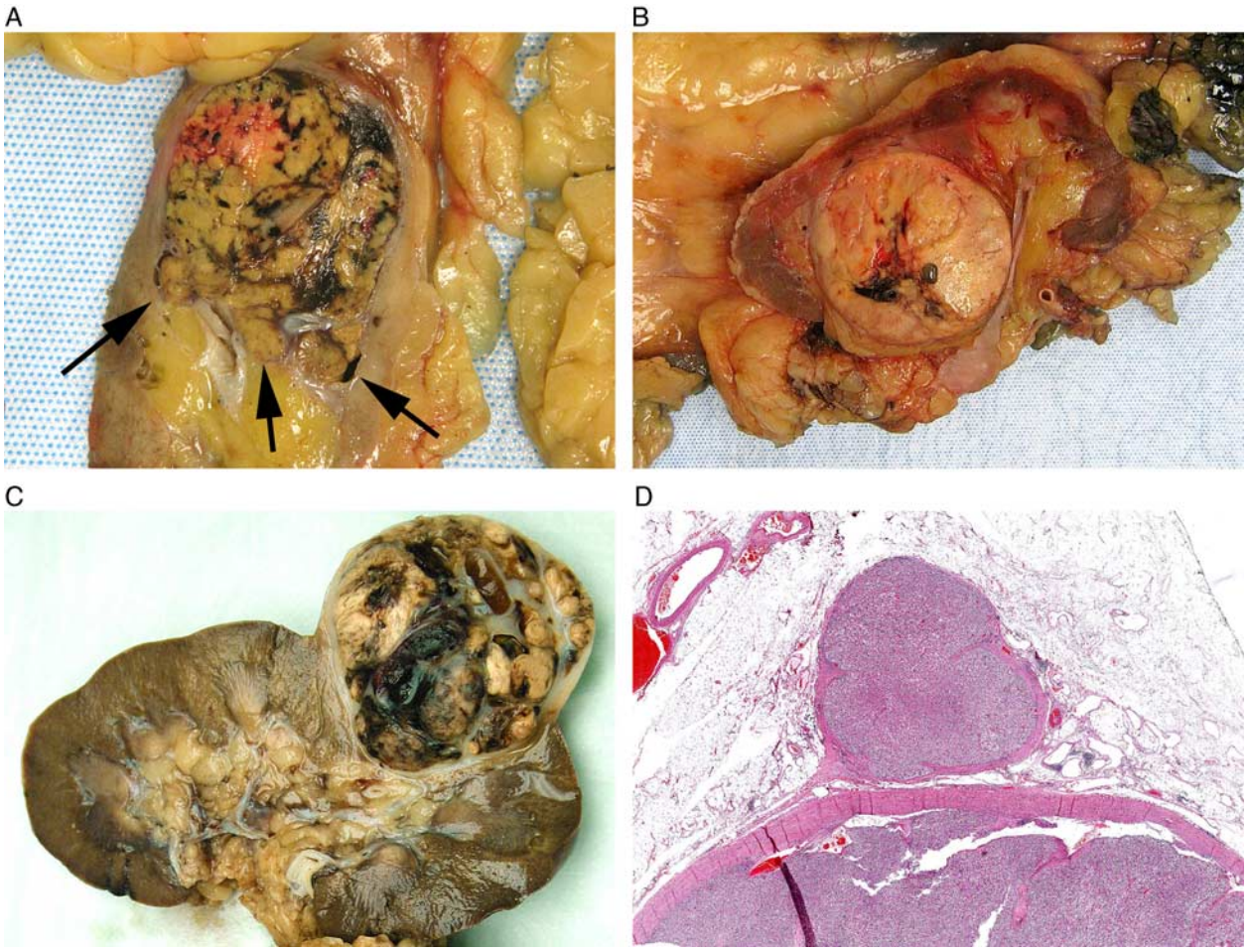

FIGURE 5. Scenarios in gross pathology and extrarenal spread: A, A gross image from question 38 demonstrates outpouchings of clear cell renal cell carcinoma into renal sinus and vascular tissue (arrows). Most participants responded that this was suspicious for vascular invasion (68%) but that histologic confirmation is required. A minority (19%) reported that this was unequivocal for vein invasion based on the gross features alone. B, For a round tumor bulging into the renal sinus, 71% of participants indicated that this was not sufficient to assign pT3a. C, For a round tumor bulging into the perinephric fat, 90% of participants indicated that this was not sufficient to assign pT3a. D, Histologically, a rounded nodule beyond the apparent renal capsule did not reach consensus for pT3a (55% yes, 45% no/equivocal).

outpouchings indeed represent venous extensions. In contrast, there was strong agreement (97%) that if this rim of tissue contains normal structures, such as tubules or glomeruli, that it does argue against invasion. Another scenario evaluated was the occurrence of a solid mass in the wall of an apparently unilocular cyst. In this setting, using the cyst size as the tumor size might increase the pathologic T stage category within pT1 or pT2 category, whereas using the solid component only might lower the pT category. This situation reached consensus (71%) that the combined cyst and mass size can be used, if the cyst appears to have a similar neoplastic lining, whereas only the solid mass size may be used if the cyst has denuded or different lining.

Regarding gross pathology, the balance of the survey results indicates that most urologic pathologists require microscopic confirmation of gross findings for increasing the stage, at least in the subtle and ambiguous cases that were tested in this survey. This included gross images of possible venous invasion, and queries regarding assessment of the vein margin. However, 58% of participants reported that they would be willing to report pT3a for a grossly convincing example of vein invasion that lacks a clear histologic lumen. Most agreed that the definition of a positive vein margin necessitates that the tumor is microscopically adherent to, or invading the vein wall at, the margin (ie, gross presence of tumor at or beyond the resected end of the vein is insufficient for positive margin).

Another peculiar feature of renal cell carcinoma is that tumors can bulge well beyond the normal contour of the kidney and can sometimes be encapsulated by a layer of normal or atrophic kidney tissue, which argues against invasion. There was strong agreement (90%) that a spherical mass bulging well into the perinephric tissue did not necessarily constitute perinephric extension; however, this decreased to 71% for a mass that bulged into the renal sinus, perhaps due to the known proclivity of clear cell renal cell

TABLE 1. Summarized Features of Cases Reaching Strong Consensus for or Against pT3a

Consensus >80% for pT3a	
Finger-like or polypoid tumor within well-defined vascular space in renal sinus (Fig. 3)	3
"Satellite" nodules with definite/probable vascular lumina in renal sinus	2
Jagged contour of tumor cells between fat cells in renal sinus (Figs. 4A-B)	2
Tumor herniating into renal sinus with possible vascular lumen	1
Nodule beyond tumor pseudocapsule in the plane of fat in renal sinus	1
Total	9
Consensus >80% against pT3a	
Finger-like protrusion with no vascular lumen, within the kidney, with no adjacent sinus fat (Fig. 2A)	1
Small nodule within tumor pseudocapsule with no definite vascular lumen	1
Finger-like protrusion into (but not beyond) renal capsule	1
Nodular bulge into perinephric fat	1
Total	4

carcinoma to invade the renal sinus[10–12] and the need for careful assessment of the possible invasion in this context.

When comparing US pathologists to non-US pathologists, there were 9 questions with marked differences; however, it is uncertain if this reflects any truly significant practice patterns. One might consider whether a potentially more litigious environment could influence diagnostic interpretations; however, due to the smaller subsets of pathologists for comparison (including only 10 non-US), even a small shift of 2 or 3 votes could make a relatively large impact in the overall percentage.

A limitation of this study, and of any study that uses the method of consensus specialist opinion, is that it does not assess the true biological behavior of the depicted cases. The main objective of the current study was to assess whether urologic pathologists have similar interpretations of specific criteria, to attempt to determine their reproducibility across a spectrum of practices. Our aim was not to assess whether the depicted foci of potential early invasion are equally prognostic as those that demonstrate unequivocal invasion. Nonetheless, practicing with substantial vigilance for detecting early invasion is important for patient prognosis, including recognition of early renal sinus or vascular invasion, and potentially discriminating the level of renal vein or vein branch extension.[13–16] One study recently demonstrated that main renal vein invasion is independently associated with worse recurrence-free survival and cancer-specific survival, when compared with segmental renal vein branch invasion.[15] This study, performed at a single institution, used reporting of general surgical pathologists, with daily availability of consultations with urologic pathology specialists. There was additional review by a single pathologist for equivocal cases. This study, however, did not clarify how the earliest state of vein branch invasion was defined.[15] Another study found that in patients with renal cancer originally diagnosed as pT1, yet who died of renal cancer, there was a substantial rate of undiagnosed vascular or renal sinus invasion upon additional sampling, compared with a control group of patients who did not die of pT1 renal cancer.[16] Therefore, it appears that it is important to carefully assess for early invasion. Such parameters likely also have substantial relevance to clinical follow-up schedules and possibly enrollment in clinical trials. Yet, apart from the current study, the data are scant concerning interobserver reproducibility and definitions of criteria for the earliest findings of invasion. We believe that highlighting these interpretations, combined with the study illustrations, may aid practicing pathologists in evaluating challenging cases. Although the low-magnification images provided (captured from whole slide images in most cases) in this study would be helpful for assessing the microscopic context, the format of providing 1 to 4 still images is different from the surgical pathology practice. Some participants indicated that in practice, they would further evaluate cases with additional gross sampling, additional histologic levels, or special stains.

Some recommendations that emerge from this work include specific scenarios where the general surgical pathologist may regard high confidence for or against extrarenal invasion, as summarized in Table 1. Particularly, these include tumors with finger-like extensions that lie within probable or definite vascular spaces, adjacent to or within the renal sinus fat, "satellite" nodules within the renal sinus fat, and tumor that intermingles with the renal sinus fat, either in a jagged configuration or with distinct nodules or herniation that is in the plane of fat. Scenarios that were considered not extrarenal spread included finger-like protrusions that remained within the kidney (without definite vascular lumen or adjacent fat, which may represent lack of continuity of the tumor pseudocapsule rather than invasion of an anatomic structure),[4] discrete nodules within the tumor pseudocapsule or renal capsule, and rounded bulge into the perinephric fat. In equivocal scenarios, we recommend a combination of reassessing the gross specimen and, if appropriate, correlation with imaging studies, consideration of recut levels of the tissue block, with or without special stains or immunohistochemistry, as relevant to the diagnostic question.

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